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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1038-1063MIS		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00870	26/07/2000	27/07/1999
International Patent Classification (IPC) or national classification and IPC C12N15/31		
Applicant CONNAUGHT LABORATORIES LIMITED		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22/02/2001	30.10.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Chavanne, F Telephone No. +49 89 2399 8399

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00870

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-55 as originally filed

Claims, No.:

1-24 as originally filed

Drawings, sheets:

1/183-183/183 as originally filed

Sequence listing part of the description, pages:

1-68, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 4, 16, 17, 20

	No:	Claims	1-3, 5-15, 18, 19, 21-24
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	
	No:	Claims	19, 20

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

IV. Lack of unity of invention

1. The present application lacks unity a posteriori within the meaning of Rule 13.1 and 13.3 PCT for the following reasons:

The common inventive concept underlying claims 1-24 can be seen in the provision of an isolated nucleic acid molecule encoding a 200 kDa outer membrane protein of a strain of *Moraxella catarrhalis*. However, taking into account that isolated nucleic acid molecules encoding such a protein from *M. catarrhalis* has already been isolated and described in the prior art (see e.g. Abstracts of the General Meeting of the American Society, Vol. 99, page 89, 1999; WO 9634960, abstract), said common concept no longer exists. Correspondingly, claims 1-24 do not relate to one single invention but to three different ones, which are not linked by a common inventive concept, namely:

Invention 1 (claims 1-3 and 5-24, partially; claim 4, completely):
an isolated nucleic acid molecule of SEQ ID No. 5 or 6, encoding a 200 kDa outer membrane protein of SEQ ID No. 7 for *M. catarrhalis* strain 4223, 5'-truncation mutants, and 5'- and 3'-truncation mutants encoding for truncated 200 kDa outer membrane proteins, recombinant vectors comprising said isolated acid molecules, host cells transformed with said vector, the expressed recombinant 200 kDa outer membrane proteins, immunogenic compositions comprising said proteins, a method of treatment based on the use of said immunogenic compositions, and a method for the production of said 200 kDa outer membrane proteins.

Invention 2 (claims 1-3 and 5-24, partially):
an isolated nucleic acid molecule of SEQ ID No. 8, encoding a 200 kDa outer membrane protein of SEQ ID No. 9 for *M. catarrhalis* strain Q8, 5'-truncation mutants, and 5'- and 3'-truncation mutants encoding for truncated 200 kDa outer membrane proteins, recombinant vectors comprising said isolated acid molecules, host cells transformed with said vector, the expressed recombinant 200 kDa outer membrane proteins, immunogenic compositions comprising said proteins, a method of treatment based on the use of said immunogenic compositions, and a method for the production of said 200 kDa outer membrane

proteins.

Invention 3 (claims 1-3 and 5-24, partially):
an isolated nucleic acid molecule of SEQ ID No. 10, encoding a 200 kDa outer membrane protein of SEQ ID No. 11 for *M. catarrhalis* strain LES-1, 5'-truncation mutants, and 5'- and 3'-truncation mutants encoding for truncated 200 kDa outer membrane proteins, recombinant vectors comprising said isolated acid molecules, host cells transformed with said vector, the expressed recombinant 200 kDa outer membrane proteins, immunogenic compositions comprising said proteins, a method of treatment based on the use of said immunogenic compositions, and a method for the production of said 200 kDa outer membrane proteins.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: Abstracts of the General Meeting of the American Society
   Vol. 99, page 89, 1999
   D2: WO 9634960

2. D1 discloses the isolation and the characterisation of a gene encoding a 200 kDa outer membrane protein from a strain of *Moraxella catarrhalis*. The nucleotide sequence encoding said protein shows a tract of 9 consecutive G nucleotides in the 5' region. D1 further mentions that for normal expression of the 200 kDa protein, the number of Gs in the G-tract has to be a multiple of 3. D1 does not specifcally mention wether the characterised nucleotide sequence has an ATG start codon about 80 to 90 bp upstream of said tract. However, the gene encoding said 200 kDa outer membrane protein has been made available (it has been cloned) and the corresponding nucleotide sequence is known. The fact that D1 does not specifically refers to the relative position of the start codon compared to that of the G-tract, does not render the isolated and purified nucleic acid molecule

of claim 1 novel over D1.
Thus, in view of D1, the subject-matter of claims 1, 2 and 5-11 cannot be considered novel.

D2 describes an isolated and purified nucleic acid molecule encoding a 200 kDa outer membrane protein of *M. catarrhalis* (example 11; figure 6). D1 further shows the presence of said protein in several different *M. catarrhalis* strains, including *M. catarrhalis* strain 4223 (example 2; figure 1). D2 discloses immunogenic compositions comprising the 22 kDa outer membrane protein (example 5), and the induction of protection against disease caused by *M. catarrhalis* (example 8). D2 further describes deletion constructs of N-terminal truncation genes encoding truncated 200 kDa outer membrane proteins. said truncation genes are under the control of the T7 promoter and after ligation into vectors allow expression of a large quantity of N-terminally truncated 200 kDa protein in *E. coli* (example 12). Thus, in view of D2, the subject-matter of independent claims 3, 5-15, 18, 19 and 21-24 is not novel. It should be noted that the expression "identifying characteristics" used in dependent claims 7-9 to try to characterise the vector of claim 5 does not refer to any technical feature, and thus, cannot be used as an element of novelty for said vector.

Therefore, claims 1-3 and 5-15, 18, 19 and 21-24 do not meet the requirements of Article 33(2) PCT.

3. The closest prior art to evaluate the inventiveness of the present application is D2. The problem to be solved by the present application can be seen in the provision of an alternative 200 kDa outer membrane protein for *M. catarrhalis*. The present application solves this problem by providing said protein from a specific strain (e.g. 4223). However, the man skilled in the art, aware of D2, which show the presence of said protein in many *M. catarrhalis* strains including strain 4223, by applying routinely used technics would isolate and characterise said protein and the nucleic acid molecule encoding it. Hence, the man skilled in the art would come to the subject-matter of claims 1 and 2 in a straightforward manner. By further applying common knowledge and commonly used technics, the man skilled in the art would also come to the subject-matter of claims 5-24. D2 further describes the expression of truncated 200 kDa outer membrane protein in *E. coli*,

and their use in immunogenic compositions to induce protection against disease caused by *M. catarrhalis*. Thus, in view of D2, the man skilled in the art, by further applying common knowledge and commonly used technics would come to the subject-matter of claims 3-24 without the need of applying any inventive skill.

Therefore, claims 1-24 do not meet the requirements of Article 33(3) PCT.

4. For the assessment of the present claims 19 and 20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

VI. Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*
WO 00/55191	21.09.2000	16.03.2000	16.03.1999

VII. Certain defects in the international application

1. The nucleotide sequence of SEQ ID No. 13 is set forth is figure 8, and not in figure 9 as mentioned in claim 3 (see page 9 of the specification).

SUMMARY OF THE INVENTION

The present invention is directed towards the provision of a recombinantly-produced purified and isolated outer membrane protein of *Moraxella catarrhalis* and other *Moraxella* strains, having an apparent molecular mass of about 200 kDa, as well as genes encoding the same from various strains of *Moraxella catarrhalis*.

In one aspect of the present invention, there is provided an isolated and purified nucleic acid molecule having (a) a nucleotide sequence set forth in Figure 3, 4 or 5 (SEQ ID Nos: 5, 6, 8, 9, 11, 12) for *Moraxella catarrhalis* strains 4223, Q8 and LES-1 respectively or the complementary sequence thereto; (b) a nucleotide sequence encoding an about 200 kDa outer membrane protein of a strain of *Moraxella catarrhalis* and having the derived amino acid sequence shown in Figures 3, 4 or 5 (SEQ ID Nos: 7, 10, 13) for *Moraxella catarrhalis* strains 4223, Q8 and LES-1 respectively; and (c) a nucleotide sequence encoding an about 200 kDa outer membrane protein of another strain of *Moraxella catarrhalis* which is characterized by a tract of consecutive G nucleotides which is 3 or a multiple thereof in length, an ATG start codon about 80 to 90 bp upstream of said tract and said tract being located between about amino acids 25 and 35 encoded by the nucleotide sequence.

The another strain of *Moraxella catarrhalis* in (c) is a strain as identified in Table 1A other than strains 4223, Q8 and LES-1 and expressing an about 200 kDa protein.

In another aspect of the invention, there is provided an isolated and purified nucleic acid molecule having a nucleotide sequence selected from the group consisting of (a) a nucleotide sequence set forth in Figure 8 (SEQ ID No: 12) for a 5'-truncation of the gene encoding an about 200 kDa outer membrane protein of *Moraxella catarrhalis* strain 4223 contained in pKS348; (b) a nucleotide sequence encoding the derived amino acid sequence set forth in Figure 9 (SEQ ID No: 13) for a N-terminal truncation of an about 200 kDa outer membrane protein of *Moraxella catarrhalis* strain 4223 produced by pKS348; (c) a nucleotide sequence set forth in Figure 21 (SEQ ID No: 45) for a 5' truncation of the gene encoding an about 200 kDa outer membrane protein of *Moraxella catarrhalis* strain 4223 contained in pQWF; (d) a nucleotide sequence encoding the derived amino acid sequence set forth in Figure 21 (SEQ ID No: 46) for a N-terminal truncation of an about 200 kDa

CLAIMS

What we claim is:

1. An isolated and purified nucleic acid molecule having a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence set forth in Figure 3, 4 or 5 (SEQ ID Nos: 5, 6, 8, 9, 11, 12) for *Moraxella catarrhalis* strains 4223, Q8 and LES-1 respectively or the complementary sequence thereto,

(b) a nucleotide sequence encoding an about 200 kDa outer membrane protein of a strain of *Moraxella catarrhalis* and having the derived amino acid sequence shown in Figures 3, 4 or 5 (SEQ ID Nos: 7, 10, 13) for *Moraxella catarrhalis* strains 4223, Q8 and LES-1 respectively, and

(c) a nucleotide sequence encoding an about 200 kDa outer membrane protein of another strain of *Moraxella catarrhalis* which is characterized by a tract of consecutive G nucleotides which is 3 or a multiple thereof in length, an ATG start codon about 80 to 90 bp upstream of said tract and said tract being located between about amino acids 25 and 35 encoded by the nucleotide sequence.

2. The nucleic acid molecule of claim 1 wherein said another strain of *Moraxella catarrhalis* in (c) is a strain as identified in Table 1A other than strains 4223, Q8 and LES-1 and expressing an about 200 kDa protein.

3. An isolated and purified nucleic acid molecule having a nucleotide sequence selected from the group consisting of:

(a) a nucleotide sequence set forth in Figure 8 (SEQ ID No: 12) for a 5'-truncation of the gene encoding an about 200 kDa outer membrane protein of *Moraxella catarrhalis* strain 4223 contained in pKS348,

(b) a nucleotide sequence encoding the derived amino acid sequence set forth in Figure 9 (SEQ ID No: 13) for a N-terminal truncation of an about 200 kDa outer membrane protein of *Moraxella catarrhalis* strain 4223 produced by pKS348,